REMARKS

A. Summary of the Claimed Invention

Broadly, the invention of the subject application is directed to a method for detecting the presence of one or more specific nucleotides at a predetermined target position in a target nucleic acid.

The method of the invention includes the step of providing an analyzable amount of the target nucleic acid in a single stranded form. The method further includes the step of hybridizing the target nucleic acid with a detection primer to form a target-nucleic-acid/detection-primer hybrid. The detection primer comprises a detection-primer nucleotide sequence, which has a primer-extension-initiation 3'-end nucleotide that constitutes a 3' end of the detection primer. The detection-primer nucleotide sequence is complementary to a primer-hybridizing nucleotide sequence of the target nucleic acid. A nucleotide in the target nucleic acid complementary to the primer-extension-initiation 3'-end nucleotide of the detection-primer nucleotide sequence defines a primer-end complement nucleotide. The primer-hybridizing nucleotide sequence of the target nucleic acid extends towards the 3' end of the target nucleic acid from the primer-end complement nucleotide. The primer-end complement nucleotide is located in the target nucleic acid at a position 3'-ward of the predetermined target position. The position of the primer-end complement nucleotide is subject to a constraint that no nucleotide of the same type as the one or more specific nucleotides to be detected be located in the target nucleic acid in any position between the position of the primer-end complement nucleotide and the predetermined target position.

The method of the invention for detecting the presence of one or more nucleotides at a target position in a target nucleic acid further includes the step of forming an extension-reaction mixture by exposing the target-nucleic-acid/detection-primer hybrid to an admixture of a polymerization agent and a plurality of nucleoside triphosphates. The nucleoside triphosphates

of the admixture include at least one deoxynucleotide and at least one chain-terminating nucleotide analogue. Each deoxynucleotide of the admixture of nucleotides triphosphates is complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary.

In one aspect, the plurality of nucleotide triphosphates of the admixture is such that, if a deoxynucleotide is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion incorporating the deoxynucleotide. In a second aspect, the plurality of nucleoside triphosphates of the admixture is such that, if a chain-terminating nucleotide analogue is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion terminated with the chain-terminating nucleotide analogue. In both aspects, the detectable nucleotide-identifier primer-extension product is detectably different from the detection primer and from any alternative primer-extension product which would be formed if a nucleotide other than said specific nucleotide were at the target position.

Finally, method of the invention for detecting the presence of one or more nucleotides at a target position in a target nucleic acid includes the step of analyzing the extension-reaction mixture for the presence or absence of the detectable nucleotide-identifier primer-extension product to detect the presence of the corresponding specific nucleotide at the target position in the target nucleic acid.

B. Summary of the Outstanding
Office Action

In the Office Action of 25 February 2003, claims 40 through 81 inclusive were rejected under 35 USC §112, second paragraph, with the assertion that the claims were indefinite for

failing to particularly point out and distinctly claim the subject matter which the applicant regarded as the invention. It was asserted that claims 40 through 50 inclusive and 61 through 71 inclusive were indefinite with the comment that the expression "the labeling moiety at the 3' end" recited in step d assertedly lacked antecedent basis. It was asserted that claims 51 through 60 inclusive were indefinite with the comment that the expression "which differs depending on whether the chain-terminating nucleotide analogue is complementary or not complementary to the defined site" assertedly did not set forth how or from what the "detectable primer extension product" differed. It was asserted that claims 61 through 71 were indefinite with the comment that the phrase "none of the chain terminating nucleotide analogues are not complementary to the defined site" contained a double negative which assertedly rendered the claims unclear. It was asserted that claims 72 through 81 were indefinite with the comment that the phrase "which differs depending on whether one of the chain terminating nucleotide analogues is complementary to the defined site or none of the chain terminating nucleotide analogues is complementary to the defined site" assertedly makes the claims unclear, assertedly because the phrase does not set forth how or from what the "detectable primer extension product" differs.

Claims 40 through 81 inclusive were rejected under 35 USC §112, first paragraph, with the assertion that the claims contained subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention.

With respect to the rejection under 35 USC §112, first paragraph, it was asserted that claims 40 through 81 inclusive were not supported by the specification and introduced new matter to the claims. With respect to claims 40 through 50 inclusive, it was asserted that the claims were drawn to a method for identifying a nucleotide at a defined site by hybridizing a primer whose 3' end bound to a nucleotide flanking the nucleotide to be detected and extending the primer in the presence of at least one deoxynucleotide and a chain-terminating nucleotide to form a detectable extension product containing a labeling moiety if the chain terminator was not

complementary to the nucleotide to be identified. With respect to claims 51 through 60 inclusive, it was asserted that the claims were drawn to the same method in which the primer was extended in the presence of at least one deoxynucleotide and a chain terminating nucleotide analogue such that a detectable product is form which differs depending upon whether or not the chain-terminating nucleotide was complementary to the defined site. With respect to claims 61 through 71 inclusive, it was asserted that the claims were drawn to the same method in which the primer extension was performed in the presence of at least one deoxynucleotide and more than one chain terminating nucleotide analogue such that a detectable primer extension product comprising a labeling moiety was formed if [none of] the chain terminators were not complementary to the defined site. With respect to claims 72 through 81 inclusive, it was asserted that the claims were drawn to the same method in which the primer extension occurred in the presence of at least one deoxynucleotide and more than one chain terminator such that the primer extension product differed depending upon whether or not the one chain terminating nucleotide was complementary to the defined site or whether none of the chain terminators were complementary.

It was asserted that the specification of the subject application did not describe the methods of claims 40 through 81 inclusive. It was asserted that the specification disclosed a method using labeled nucleotides that matched the variable nucleotide to detect the variable nucleotide in the target nucleic acid. It was asserted that the specification further disclosed the introduction of an affinity moiety into the target nucleic acid during amplification of the target nucleic acid prior to the detection steps for the variable nucleotide to allow immobilization of the target nucleotide acid. It was asserted that the specification described the separation of the amplified target nucleic acid from the amplification mixture. It was asserted that the specification of the application described a detection step primer and disclosed that it could be modified to have an affinity moiety different from the affinity moiety used during amplification, but disclosed that the preferred detection primer was unmodified. With respect to the description

of the extension of the detection primer, it was asserted that the specification disclosed that the nucleotide mixture could be one or more nucleoside triphosphates, but assertedly included at least one labeled or modified nucleotide which was either a labeled dNTP or a dideoxynucleotide (ddNTP). It was asserted that the specification disclosed that the dNTP or ddNTP was labeled with a detectable label or modified to have an attachment moiety capable of binding to a detectable label. It was asserted that particular embodiments of the invention disclosed in the specification concerned: a) a method in which only labeled ddNTPs corresponding to the variable nucleotide were added; b) a method in which labeled dNTP corresponding to the variable nucleotide was added and that unlabelled ddNTP was preferably included; c) a method which used two or more different, differently labeled dNTPs corresponding the variable nucleotide; d) a method using a detection step primer which was n nucleotides away from the variable nucleotide and using unlabeled dNTPs which were complementary to the n nucleotides between the primer and the variable nucleotide and labeled dNTPs corresponding to the variable nucleotide which could be substituted for labeled ddNTPs; and (e) a method in which two or more variable nucleotides were identified which required the use of at least two different detection primers which hybridized 3' of each of the variable nucleotides to be identified. It was asserted that specific examples in the specification of the application exemplified labeling with radiolabels, enzyme labels and fluorescent labels.

It was asserted that the specification did not describe a method in which extension occurred in the presence of at least one deoxynucleotide and one or more chain terminating oligonucleotides where neither the diosynucleotide nor the chain terminator was detectably labeled. It was further asserted that the specification did not teach labeling the primer extension product after the deoxynucleotide and/or chain terminator was incorporated, but that such a method was now assertedly encompassed by the claims. It was asserted that the specification was specific that either the deoxynucleotide or chain terminating nucleotide analogue was labeled and the means by which the variable nucleotide was detected. It was asserted that the

specification did not describe broadly the concept of forming a primer extension product which contained a label at the 3' end when the chain terminator was not complementary to the variable nucleotide. It was asserted that the specification disclosed that a labeled nucleotide was used when the chain terminator was not complementary to the variable base. It was asserted that the specification was directed to a method to detect a nucleotide of known sequence so that the base on the deoxynucleotides and the chain terminators for use in the method was assertedly predetermined. It was asserted that whether or not the deoxynucleotide or the chain terminator would hybridize to a defined site was also predetermined. It was asserted that the specification disclosed that either the deoxynucleotide or the chain terminator was labeled directly or indirectly in the method of the specification. It was asserted that the specification did not support the method of claims 40 through 81 inclusive which assertedly recited that the primer was extended in the presence of deoxynucleotide or chain terminator which might or might not be labeled.

Claims 40 through 81 inclusive were rejected in the Office Action of 25 February 2003 under the doctrine of obviousness-type double patenting as assertedly unpatentable over claims 1 through 26 inclusive of United States patent No. 6,013,431 ("the '431 patent"). Although it was conceded in the Office Action that the conflicting claims were not identical, it was asserted that the conflicting claims were not patentably distinct from one another because the claims of the subject application contained overlapping subject matter with the claims of the '431 patent. It was asserted that the claims of the '431 patent were drawn to a method for determining a nucleotide variation at a defined site using a primer which hybridized at its 3' end to the nucleotide flanking the nucleotide variation and extending in the presence of a mixture containing at least one labeled deoxynucleotide and at least one dideoxynucleotide. It was asserted that the claims of the subject application were drawn to the same method assertedly in which extension occurred in the presence of a mixture containing at least one deoxynucleotide and one or more chain terminating nucleotide analogues in which the deoxynucleotide or chain terminator nucleotide might or might not be labeled. It was asserted that because the claims of

the subject application and those of the '431 patent both included a method in which the deoxynucleotide was labeled, the claims of the '431 patent and the claims of the subject application contained overlapping subject matter.

C. Summary of the Present Amendments
and Request for Reconsideration

Claims 40 through 81 inclusive have been cancelled without prejudice in the present reply and new claims 82 through 101 inclusive have been substituted for them.

New claims 82 through 101 inclusive find support, for example, in the specification of the application as filed at page 7, line 10 though page 8, line 14; page 9, line 25 through page 11, line 19; and page 12, line 13 through page 20, line 16 and in the drawings of the application as filed. It is submitted that none of new claims 82 through 101 inclusive constitutes new matter.

Submitted with the present reply is a Fee Transmittal form for fiscal year 2004 in which the extra claims fee for the amendments of the present reply are calculated on the basis of a total number of claims previously paid for of 46. When the subject continued prosecution application was initially submitted on 26 September 2002, the total number of claims for the application indicated on an accompanying Fee Transmittal form for fiscal year 2002 was 42. However, in fact, a total of 46 claims were submitted with the application and the number 42 noted on the accompanying Fee Transmittal form was the result of an inadvertent error in counting multiply dependent claims. The Fee Transmittal form accompanying the filing papers for the continued prosecution application of 26 September 2002 authorized the Commissioner to charge any additional fees during the pendency of the application to deposit account No. 11-0171. Thus, by operation of the authorization to charge additional fees to the deposit account, the correct total of 46 claims for the application should have been paid as of the time the application was filed. In a telephone conference on or about 26 August 2003 with Examiner Souaya in charge of the subject application, the undersigned attorney brought to her attention the matter of the incorrect number

of claims on the Fee Transmittal form accompanying the filing papers for the subject application and the authorization on the form to charge any additional fees to the deposit account. The Examiner kindly agreed to enter a debit charge to the deposit account noted above for the four miscounted claims in the application on the computer system of the Patent and Trademark Office. The purpose of the present paragraph is to make of record the telephone conference in question and to request verification that all required fees for the subject application have been paid.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. The Rejection Under 35 U.S.C. § 112, First Paragraph

It is submitted that there is ample support in the specification of the subject application as originally filed for the claims of the application, particularly new claims 82 through 101 inclusive.

At page 7, lines 10 through 12 of the subject application as filed in the section entitled "Summary of the Invention," it is stated that:

> The method of detection of the variable nucleotide(s) is based on primer extension and incorporation of detectable nucleoside triphosphates in the detection step. By selecting the detection step primers from the region immediately adjacent to the variable nucleotide, this variation can be detected after incorporation of as few as one nucleoside triphosphate.

The quoted description of the invention in the application as filed does not require that the "detectable nucleoside triphosphates" incorporated in the detection step of the method for detecting variable nucleotide(s) of the invention be labeled with a detectable label or be modified to include an attachment moiety capable of binding a detectable label. Significantly in this regard, at page 17, lines 1 through 5 of the application as originally filed, the term "labelled

nucleoside triphosphate" – not the term "detectable nucleoside triphosphate" used in the description of the invention quoted above – is expressly defined to refer to a nucleoside triphosphate labeled with a detectable label or modified to comprise an attachment moiety capable of binding a detectable label. [Underlining added.]

New independent claim 83 of the subject application is directed to a method for detecting the presence of one or more specific nucleotides at a predetermined target position in a target nucleic which includes the step, among others, of forming an extension-reaction mixture by exposing a target-nucleic-acid/detection-primer hybrid to an admixture of a polymerization agent and a plurality of nucleoside triphosphates. The nucleoside triphosphates of the admixture include at least one deoxynucleotide and at least one chain-terminating nucleotide analogue. Each deoxynucleotide of the admixture of nucleotides triphosphates is complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary. The plurality of nucleotide triphosphates of the admixture of the method of new claim 83 is specified to be such that, if a deoxynucleotide is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion incorporating the deoxynucleotide. The detectable nucleotide-identifier primer-extension product is specified to be detectably different from the detection primer and from any alternative primer-extension product which would be formed if a nucleotide other than said specific nucleotide were at the target position.

It is submitted that new independent claim 83 is supported by the specification of the subject application as originally filed.

Reasoning analogous to that applied above to new claim 83 applies with respect to new independent claim 86 and that therefore new claim 86 is supported by the specification of the subject application as originally filed.

New independent claims 82 and 85 are each directed to a method for detecting the presence of one or more specific nucleotides at a predetermined target position in a target nucleic which includes the step, among others, of forming an extension-reaction mixture by exposing a target-nucleic-acid/detection-primer hybrid to an admixture of a polymerization agent and a plurality of nucleoside triphosphates. New claim 82 specifies, among other things, that the nucleoside triphosphates of the admixture include at least one deoxynucleotide defining a labeled deoxynucleotide comprising a detectable label or an attachment moiety capable of binding a detectable label. New claim 85 specifies, among other things, that the nucleoside triphosphates of the admixture include at least one chain-terminating nucleotide analogue defining a labeled chain-terminating nucleotide analogue comprising a detectable label or an attachment moiety capable of binding a detectable label. It is submitted that both new claims 82 and 85 are fully supported by the specification of the subject application as originally filed.

New claims 84 and 87 through 101 inclusive are dependent claims which depend upon one or more of independent new claims 82, 83, 85, or 86. It is submitted that each of new claims 84 and 87 through 101 inclusive finds support in the subject application as originally filed.

For the reasons set forth above, it is submitted that each of new claims 82 through 101 inclusive finds support in the subject application as filed and does not constitute new matter. It is therefore submitted that a rejection of any of the new claims under 35 USC §112, first paragraph, would be unwarranted.

E. The Rejection Under 35 U.S.C. § 112,
Second Paragraph

Although it is submitted that claims 40 through 81 inclusive of the subject application were completely clear and definite and would have been understood by a person of ordinary skill in the art as of the effective filing date of the application with the specification and drawings of the application as filed at hand, claims 40 through 81 inclusive have been cancelled without

prejudice in the present reply and new claims 82 through 101 inclusive substituted for them. New claims 82 through 101 inclusive were drafted with the comments in the Office Action of 25 February 2003 with regard to the rejection under 35 USC §112, second paragraph, in mind.

In particular, the recitation of "the labeling moiety at the 3' end" objected to in the outstanding Office Action with respect to claims 40 through 50 inclusive and 61 through 71 inclusive was not used in any of new claims 82 through 101 inclusive submitted in the present reply. The double-negative expression objected to in the Office Action with respect to claims 61 through 71 inclusive was not employed in any of new claims 82 through 101 inclusive.

New independent claim 83 of the subject application is directed to a method for detecting the presence of one or more specific nucleotides at a predetermined target position in a target nucleic which includes the step, among others, of forming an extension-reaction mixture by exposing a target-nucleic-acid/detection-primer hybrid to an admixture of a polymerization agent and a plurality of nucleoside triphosphates. The nucleoside triphosphates of the admixture include at least one deoxynucleotide and at least one chain-terminating nucleotide analogue. Each deoxynucleotide of the admixture of nucleotides triphosphates is complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary. The plurality of nucleotide triphosphates of the admixture of the method of new claim 83 is specified to be such that, if a deoxynucleotide is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion incorporating the deoxynucleotide. The detectable nucleotide-identifier primer-extension product is specified to be detectably different from the detection primer and from any alternative primer-extension product which would be formed if a nucleotide other than said specific nucleotide were at the target position. In new claim 83, therefore, the detectable nucleotide-identifier primer-extension product is specified to be different <u>from</u> the detection primer and <u>from</u> any alternative primer-extension product which would be formed if a nucleotide other than

said specific nucleotide were at the target position in a manner which constitutes a detectable difference.

New claim 86 includes parallel language calling for a detectable nucleotide-identifier primer-extension product to be different from a detection primer and from any alternative primer-extension product which would be formed if a nucleotide other than said specific nucleotide were at the target position in a manner which constitutes a detectable difference.

It is submitted that each of new claims 82 through 101 inclusive – specifically including new claims 83 and 86 – meets the standards of particularity and distinctness of the second paragraph of 35 USC §112 and that a rejection of any of new claims 82 through 101 inclusive under 35 USC §112, second paragraph, would be unwarranted.

F. The Double-Patenting Rejection

The attorneys for the applicants respectfully traverse the rejection of claims 40 through 81 inclusive of the subject application as unpatentable over claims 1 through 26 inclusive of the '431 patent under the doctrine of obviousness-type double patenting and submit further that a rejection of any of new claims 82 through 101 inclusive as unpatentable over claims of the '431 patent would be unjustified.

The rejection under the doctrine of obviousness-type double patenting in the Office Action of 25 February 2003 was a provisional double patenting rejection since none of the claims of the subject application had been allowed. It would be premature to consider submitting a terminal disclaimer with respect to the '431 patent in the subject application in advance of the allowance of any of the claims of the application.

G. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended fully meet the standards of 35 U.S.C. § 112, first and second paragraphs, and are

patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

Attorneys for the Applicants

by _____
J. David Ellett, Jr.
Reg. No. 27,875

Telephone No.: (212) 813-1600